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# Clinical Update in Immunoglobulin Therapy for Primary Immunodeficiency Diseases

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# Clinical Update in Immunoglobulin Therapy for Primary Immunodeficiency Diseases

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## Abstract

Immunoglobulin therapy represents a life saving intervention for many patients with primary immunodeficiency disease (PIDD). While this therapy has existed and has been in use for more than 60 years, the preparations themselves and our understanding of how they are applied to patients to enhance outcomes has continually evolved. This update will focus upon the currently available immunoglobulin preparations and how they can be used to optimize patient outcomes.

## History and Diagnoses

Primary antibody deficiencies as a PIDD are those in which the major impact is upon the production and maintenance of quality antibodies against specific antigens. These disorders have their roots in several places. Perhaps most importantly is the original publication of Bruton in the Journal Pediatrics in 1952 (1). Here the first case of agammaglobulinemia was described and along with it the reconstitution of immunoglobulin in the patient through immunoglobulin therapy. In this report, Bruton provided a relatively crude preparation of immunoglobulin via the subcutaneous route. He documented restoration of serum immunoglobulin levels and described a clinical benefit for the patient. In the almost 60 years that have elapsed since this initial publication, an entire field of PIDD has evolved as well as tremendous innovation in the treatment of PIDD patients.

PIDD presently represents a compilation of greater than 150 different diseases according to the International Union of Immunological Societies (IUIS) expert panel review (2). The list of diseases characterized as a PIDD has expanded substantially in recent years and will most certainly continue to expand in years to come. Presently, more than 60 of the IUIS categorized PIDD affect the production of antibodies. In considering the replacement of antibodies therapeutically, however, it is impractical to have 60 different guidelines and approaches for using immunoglobulin in PIDD. This is especially true as the number of individual antibody deficiency diagnoses continues to expand even further. For this reason, it is logical as we move into the future, to utilize a smaller number of phenotypic categories that will account for and encompass the individual PIDD diagnoses affecting antibody production. It has been proposed to consider the antibody deficiencies according to 4 phenotypic categories (3). These are presented in Table 1 and rely upon three basic phenotypes: 1) presence of B cells; 2) quantity of antibody; and 3) quality of antibody. This in essence represents an expanded approach previously published by a working group of the American Academy of Allergy, Asthma and Immunology (AAAAI) (4). Since immunoglobulin replacement therapy is with IgG, the consideration of antibody in this present and the previous schema is limited to IgG.

**TABLE 1**

Adapted from Stiehm, Orange, Ballow, et. al. Adv. Pediatr. 2010 57:185-218

| CATEGORY | B CELLS | IgG QUANTITY | IgG QUALITY *(antigen-specific antibody)* | DIAGNOSTIC EXAMPLES |
|---|---|---|---|---|
| I | Absent | Absent | Absent | • Agammaglobulinemia<br>• SCID |
| II | Present | Low | Low | • Hyper IgM<br>• CVID<br>• NEMO deficiency (subset) |
| III | Present | Normal | Low | • Specific Antibody Deficiency<br>• NEMO deficiency (subset)<br>• Subclass deficiency with specific antibody defect |
| IV[a] | Present | Low | Normal | • Transient hypogammaglobulinemia of infancy<br>• Primary hypogammaglobulinemia |

[a]*Documentation of specific antibody function should be performed in these individuals and if impaired should prompt their being considered for a category II diagnosis.*

The first phenotypic category is when a patient lacks B cells, which of course are required for antibody production. In this case, there is inappropriate antibody quantity and quality. Examples include agammaglobulinemia and severe combined immunodeficiency (SCID), both of which can be due to a variety of distinct genetic causes, including some cases that have yet to be genetically defined.

The second category is when B cells are present, but both antibody quality and quantity are abnormal. Examples here include common variable immunodeficiency (CVID) and the hyper-IgM syndrome. Again, there are multiple distinct genetic causes for these, but CVID in the great majority remains without a genetic mechanism. Since it is hypothesized that CVID, like many of the antibody deficiencies, results from multifactorial and multiple individual genetic etiologies, it is unlikely that there will ever be a singular genetic mechanism. For this reason, the use of phenotypic categories remains relevant.

The third category is when B cells and the quantity of antibody are normal, but the quality is not. Examples here include the phenotypic diagnosis referred to as specific antibody deficiency (SAD), or specific antibody deficiency with normal immunoglobulins (SADNI). While the vast majority of genetic pathogenesis of this diagnosis is unknown, a number of known genetic immunodeficiencies are known to present with this phenotype, such as NEMO deficiency (5).

The fourth category is one in which both B cells and antibody quality are present, but the total quantity of immunoglobulin is decreased. Similar to the previous category, most of these are without genetic mechanisms, but the category is most typically represented by primary hypogammaglobulinemia or transient hypogammaglobulinemia of infancy. Again there are genetic syndromes that are significantly associated with these such as the association between 22q11 microdeletion and CHARGE syndromes and transient hypogammaglobulinemia of infancy (6).

A separate consideration not listed as a separate category is when B cells and antibody quality are intact, but the quantity is deficient in one of the three major IgG subclasses (IgG1, IgG2, or IgG3). While this group is unclear from a mechanistic standpoint, many patients have problems typical of humoral immunodeficiency and it is likely that explanations will emerge in the future. Interestingly, this group has represented an initial diagnosis for some patients who ultimately were diagnosed with specific genetic conditions, such as NEMO (7).

Another potential category not listed on the table represents a patient who has hallmark infections of humoral immunodeficiency, but has normal B cells, antibody quality and quantity using currently available testing technologies. While this category does not represent a humoral immunodeficiency, it is a population worth following as future laboratory innovations may define specific quality defects within this group that may allow them to be placed into the third category. They may also represent patients "in evolution" who might eventually develop detectable humoral abnormalities. This, unfortunately, is likely to be consistent with the long diagnostic delays found in certain diagnoses such as CVID (8). This potential category also might contain patients with defects elsewhere in the immune system, such as in the innate immune system (i.e., IRAK4 deficiency), who are in need of more intensive investigation.

With regards to the appropriateness of providing immunoglobulin replacement therapy to patients with humoral PIDD in consideration of the abovementioned phenotypic categories, the evidence underlying these and recommendations for doing so is the topic of other articles and documents (reviewed in (4, 9)). There are, however, certain considerations that should be respected and are worth pointing out here. In particular, there are some diagnoses for which it is imperative to supply immunoglobulin replacement immediately upon diagnosis and not stop therapy for any additional diagnostic purposes. These would include SCID, agammaglobulinemia, and hyper-IgM. A single cessation of therapy for others may be appropriate for diagnostic confirmation, but this depends on clinical circumstances. It is not appropriate to institute more than one, or continual cessations of therapy for diagnostic purposes. Additional discussion of the individual diagnoses and decision to institute replacement therapy, again is the topic of other documents (4, 9-11).

## Ig Preparations

Once a decision to replace immunoglobulin has been made, there are a significant number of options faced by the prescribing clinician. Ig therapy is not a binary or a "one-size fits all" decision. In the author's opinion, it is incorrect to consider Ig therapy as generic and non-malleable, or to uniformly apply inflexible formulary limitations. It is important to appreciate the value of the decision in prescribing Ig therapy and for the clinician to take an active role in the process, since the outcome can have major impact for the patient. Some of the decisions relate to how Ig therapy is administered, which will be covered in greater detail in subsequent sections. In this section, the initial decisions available to a prescriber regarding the Ig preparations themselves are covered.

Perhaps the very first choice available to a prescriber after a decision is made to provide Ig replacement therapy to a patient, regards the route of administration of the Ig. Specific Ig preparations are approved by the U.S. FDA for use in PIDD to be administered by intravenous, subcutaneous or intramuscular routes (Table 2). Details and considerations relevant to the particular routes of therapy will be raised later. As for the Ig preparations themselves, they all share certain features. Importantly there are limited ranges of acquisition and manufacturing processes from which polyclonal Ig can be produced from human plasma (polyclonal Ig defines an Ig preparation having a diversity of

specificities). Furthermore, there are guidances set by the FDA (examples within (12)) as well as voluntary standards generated by the plasma industry (summaries within (13)). A detailed discussion of these is outside the focus of this present review, but there are several of these common features worth considering. First, the FDA advises that polyclonal Ig for replacement therapy be generated from pooled plasma from between 15,000 and 60,000 donors and that all plasma donations used are obtained from within the U.S. This is important for providing the diversity of antibody specificity that is needed for defense against a wide variety of infectious diseases to which a PIDD patient could be exposed, as well as to ensure specificity against infectious challenges that would be experienced in the U.S.

Another feature worthy of mention is that most plasma collected in the U.S. for use in making polyclonal Ig is derived from commercial plasma collection centers and not whole blood donations. In these plasma centers, individuals enter into a longitudinal relationship with a particular center to undergo plasmapheresis. While individual donors are minimally compensated for their time, this relationship provides the opportunity for careful follow-up of the individual donor. All donors are carefully screened and tested to ensure lack of risks for transmissible diseases and if any donors are identified as presenting risk, they are added to a national database to prevent them from donating. Importantly, a voluntary plasma industry standard is to hold donations for 60 days prior to using them in producing Ig in order to provide an additional time window for and margin of safety in the testing process.

The specific products available for intravenous (IV), subcutaneous (SC) or even intramuscular (IM) use in the U.S. has gradually changed in recent years. At the time of the writing of this document there were 9 products indicated for IV use in PIDD, 3 for SC use and 1 for IM use. IM is not a preferred route of administration for PIDD in the present era as it is difficult to provide adequate dosing and as such results in inferior outcomes (14).

**TABLE 2**

Polyclonal Ig products currently available in the US

| Product | Use | Form | Stabilizer | IgA | Osmolarity/ Osmolality | Sodium | Storage | Manufacture |
|---|---|---|---|---|---|---|---|---|
| Carimune NF | IV | Lyophilized 3 to 12% | Sucrose | 720 µg/mL | 192 - 1074 mOsm/kg | <20 mg sodium chloride per gram of protein | RT (24m) | CSL Behring |
| Flebogamma DIF 5% | IV | 5% Liquid | Sorbitol | <50 µg/mL | 240-370 mOsm/kg | Trace | RT (24m) | Grifols |
| Flebogamma DIF 10% | IV | 10% Liquid | Sorbitol | <100 µg/mL | 240-370 mOsm/kg | Trace | RT (24m) | Grifols |
| Gammagard Liquid | IV | 10% Liquid | Glycine | <37 mcg/ml | 240-300 mOsm/kg | None Added | RT (12m) at 25c 4° (36m) | Baxter |
| Gammagard SD 5% | IV | Lyophilized | Glucose | <1.0 – 2.2 mcg/mL | 636 mOsm/L 5% 1250 mOsm/L 10% | 8.5 mg/mL sodium chloride | RT (24m) at 25° | Baxter |
| Gammunex-C | IV or SC | 10% Liquid | Glycine | 46 µg/mL | 258 mOsm/kg | Trace | RT (9m) 4° (36m) | Talecris Biotherapeutics |
| Octagam | IV | 5% Liquid | Maltose | <100 µg/mL | 310-380 mOsm/kg | ≤30 mmol/L | RT (24m) | Octapharma |
| Privigen | IV | 10% Liquid | Proline | ≤25 µg/mL | isotonic (320 mOsmol/kg) | Trace | RT (24m) | CSL Behring |
| Gammaplex | IV | 5% Liquid | Sorbitol Glycine | <10 µg/mL | 460-500 mOsm/kg | 30 – 50 mmol/L | RT (24m) | BPL |
| Hizentra | SC | 20% Liquid | Proline | ≤50 µg/mL | 380 mOsmol/kg | Trace (≤10 mmol/L) | RT | CSL Behring |
| Vivaglobin | SC | 16% Liquid | Glycine | <1700 µg/mL | 445 mOsm/kg | 3 mg/mL | 4° | CSL Behring |
| Gammastan | IM | 15-18% Liquid | Glycine | Not Measured | Not Available | 0.4 - 0.5% | 2-8°C (36-46°F) | Talecris Biotherapeutics |

Of the FDA-licensed SC products, the three available are quite different. The original 16% SCIG has characteristics similar to older IM preparations of Ig. The newer SCIG products are a 10% IVIG product now licensed for SC usage (15), or a more concentrated 20% preparation with characteristics similar to other IVIG preparations (16). All have been used effectively, but the more concentrated products may offer the advantage of allowing for the provision of more Ig into individual infusion sites. The 10% product offers the advantage of being the very same preparation used intravenously, thus potentially providing some flexibility in route of administration. It is likely that other Ig products will be approved for SC use by the FDA soon, and will have specific characteristics of their own worth considering.

Regarding the IVIG products available for PIDD patients, however, there is a larger choice as well as substantial variability in their characteristics (see Table 2). Some of these are going to be relevant to particular patients and centers. This topic is the subject of several published works (17-20), but is reviewed here in brief. Firstly, there are both liquid and lyophilized products available, but recent trends have been in increasing numbers of the former and decreasing numbers of the latter. Some of the liquid products have shorter shelf lives at room temperature, which is worth considering in maintaining an inventory of IVIG. Presently there are only two concentrations of liquid IVIG products available: 5 and 10%. The 5% products include more free water per gram of Ig, which may be of relevance to patients requiring water restriction. Similarly some of the products have higher sodium content and osmolality than others, which may present increased risk to patients with cardiovascular disease and to small infants and should be considered on a patient-specific basis.

The Ig products use different additives to stabilize the Ig in monomeric format, including both sugars and amino acids. One of the sugar stabilizers used is glucose, which might be inappropriate to administer to a diabetic patient. Sucrose is also used as a stabilizer for one product and has been disproportionally associated with renal adverse events (21). Consequently, this product may be inappropriate for patients with a preexisting renal condition. Many newer Ig products contain an amino acid as a stabilizer, which may be a relevant consideration in rare patients with a metabolic disorder in whom limiting intake of particular amino acids may be important. An example would be avoiding the use of proline-stabilized Ig in patients with hyperprolinemia.

Finally, the different IVIG products contain varying amounts of IgA. While relatively low in all products, concern exists in a minority of IgA-deficient patients regarding reactivity to IgA. In this light, exceedingly rare severe reactions against IgA have been reported (22). While it is the author's experience that most IgA deficient patients tolerate most IVIG products, it is an issue worth considering in appropriate cases.

To summarize, the choice of an IV or SC Ig product is a significant decision and will define, in large part, the patient experience. This decision must be matched to specific patient needs and situations (discussed in detail below). The specific choice of which products to use is far less important, although critically relevant for a subset of patients. Knowledge of individual patient needs and conditions is relevant to the product selection and should be considered. What is far more important, however, is when possible advocating for a patient stably receiving a particular immunoglobulin product to continue to receive that product. Immune Deficiency Foundation patient survey data have identified that 34% of adverse reactions to IVIG occur during product changes (23). This increased risk with product changes has been reported by others as well (24). For these reasons, at the author's institution product changes are performed under physician supervision and are held to be of higher risk. Consistency of application and the "non-generic" status of an individual IVIG is one of the "Eight Guiding Principles" of IVIG therapy for PIDD (Table 3 – principle #8), and should be applied to patients wherever possible.

## Standards in IVIG Therapy

The licensing information available for the different IVIG products is quite variable and likely relates to the approaches utilized at the particular times the licensing studies were conducted. There are, however, certain standards of IVIG therapy that are important to apply to patients receiving treatment for PIDD. These are reflected in the "Eight Guiding Principles" of IVIG therapy for PIDD from the AAAAI (25) (Table 3). Relevant to the present discussion, it is worth elaborating upon principles 3-6; dose, interval, trough levels, and site of care.

The dosages used for treatment of PIDD with antibody deficiency do relate to the optimization of therapy (as discussed in the next section), but in the modern era, are represented by initial doses of 400-600mg/kg for a newly diagnosed patient. According to the survey of specialist practice conducted by the AAAAI, the most common initial dosage applied was that of 400mg/kg (26). Focused immunologists, however, who devote more than 10% of their clinical practice to PIDD, are more likely to utilize higher initial doses of IVIG. Using initial doses less than this, however, relates to largely antiquated experience or research, and in the present environment would be suboptimal in light of practice guidelines and expert recommendations (4, 9, 10).

Although a number of studies have been devoted to specific dosages of IVIG, far fewer have evaluated specific intervals of dosing. That said, standard therapy and that consistent with product labeling includes dosing every 3 or 4 weeks. Some patients will require even more frequent intervals to achieve clinical effect. As individual patients have distinct pharmacokinetics of IVIG, it is difficult to presently predict which patients require more or less frequent regimens. It is inappropriate, given the present burden of

**TABLE 3**

The Eight Guiding Principles of Ig Therapy in PIDD[1]

| |
|---|
| 1) **Indication** - IVIG therapy is indicated as replacement therapy for patients with PI characterized by absent or deficient antibody production. This is an FDA-approved indication for IVIG, for which all currently available products are licensed.[2] |
| 2) **Diagnoses** - There are a large number of PI diagnoses for which IVIG is indicated and recommended. Many have low total levels of IgG, but some have a normal level with documented specific antibody deficiency. |
| 3) **Frequency of IVIG Treatment** - IVIG is indicated as continuous replacement therapy for primary immunodeficiency. Treatment should not be interrupted once a definitive diagnosis has been established. |
| 4) **Dose** - IVIG is indicated for patients with primary immunodeficiency at a starting dose of 400-600 mg/kg every 3-4 weeks. Less frequent treatment, or use of lower doses, is not substantiated by clinical data. |
| 5) **IgG Trough Levels** - IgG trough levels can be useful in some diagnoses to guide care but are NOT useful in many and should NOT be a consideration in access to IVIG therapy. |
| 6) **Site of Care** - The decision to infuse IVIG in a hospital, hospital outpatient, community office, or home based setting must be based upon clinical characteristics of the patient. |
| 7) **Route** - Route of immunoglobulin administration must be based upon patient characteristics. The majority of patients are appropriate for intravenous and a subset for subcutaneous therapy. |
| 8) **Product** - IVIG is not a generic drug and IVIG products are not interchangeable. A specific IVIG product needs to be matched to patient characteristics to insure patient safety. A change of IVIG product should occur only with the active participation of the prescribing physician. |

[1] *As reproduced from the AAAAI IVIG toolkit (http://www.aaaai.org/members/resources/initiatives/ivig.stm) – weblink valid as of November 2010.*
[2] *Additional information regarding and justification for the individual guiding principles can be found within the IVIG toolkit using the above weblink*

evidence and clinical studies to provide IVIG therapy to patients at intervals less frequently than 4 weeks.

A level of IgG evaluated in patient blood at the end of an infusion cycle is known as a "trough" IgG level. Presently, different payors in the U.S. have different requirements for obtaining these IgG trough levels. It is unclear what the benefit is of obtaining trough levels as they are not a surrogate for clinical status and each patient is likely to have their own specific trough level for which they are optimally maintained. In that respect, current standards in this arena are changing (see next section), but previously published recommendations are for minimal IgG trough levels of 500mg/dl and optimal trough levels of 800mg/dl (4).

The site of care for administration of Ig is another important standard of therapy that may not be given due consideration by payors and those making decisions on behalf of patients. There can be quality of life benefits for patients to receive IVIG in the home care environment (27) and this warrants due consideration. When provided by an agency with specialized expertise employing nursing and pharmacy professionals experienced in home-based provision of IVIG, the practice can be safe and effective. The home environment, however, should be reserved for the lowest complexity patients and those without a history of infusion reactions. Patients who are complicated and/or have a history of reactions are not necessarily good candidates for home based therapy and may be more appropriate for sites of care having higher levels of supervision, such as the physician office or hospital-based infusion center. Patient preference and comfort level for particular sites of care should also be considered and honored whenever possible.

A final standard for consideration in IVIG therapy is that of intravenous access. Some physicians and patients have a preference for the use of implantable catheters to ensure easy IV administration. This provides potential time savings for patients and can reduce the trauma and stress associated with obtaining peripheral IV access. In fact, many immunologists who are focused in the care of PIDD patients do recommend placement and use of implantable catheters for the administration of IVIG. This recommendation, however, is a topic of debate and certain guideline documents do not recommend the use of these devices solely for the use of administering IVIG to PIDD patients (4, 9). The reasons cited are threefold. First, that implanted catheters present a risk of infection (28), which is theoretically greater in the immunodeficient patient. As a result, the devices need to be cultured for colonization and patients presumptively treated for infection when a significant fever occurs. Second, that the devices have a failure rate and necessitate surgical procedures for placement and replacement, which are associated with slight but measurable risks (29). Third, that indwelling catheters carry the risk of thrombus formation (30). This last issue is of specific concern to

the PIDD patient in that IVIG itself caries the risk of thromboembolism (31) and is a warning stated in IVIG product labeling. Therefore, providing a drug having thromboembolic risks through a thrombogenic device is theoretically concerning, as thrombotic complications can be serious and present major health challenges to PIDD patients. While further specific data based upon patient outcomes in PIDD is desperately needed, it is the practice of the author to not place indwelling catheters in PIDD patients for the purpose of IVIG administration and to recommend removal of indwelling catheters to patients who have had them placed by other physicians.

## Optimizing Outcomes with IVIG

Although the abovementioned standards for IVIG therapy can be used to guide therapy, they do not necessarily ensure provision of optimal therapy. To reiterate a point raised earlier, Ig therapy for PIDD should not be viewed as a binary decision and access to therapy does not always equate with optimal therapy. There are a number of opportunities and data available to the clinician that can facilitate the optimization of Ig therapy to improve outcome for the PIDD patient. Importantly, each patient needs to be viewed individually as the performance of a specific Ig regimen will differ from patient to patient and is in part a feature of patient-specific pharmacokinetics of IgG. The same dose given to two different, similarly sized PIDD patients can result in two different peak and trough Ig levels. There clearly are other factors that influence outcome as well, since a given Ig dosage or trough level may be highly effective in one patient, but ineffective in a distinct and even similarly sized patient (32).

At present it is not possible to predict which patients are going to require which doses and trough levels to have the lowest possible incidence of infections. This may change in the future as certain variables like Fc receptor polymorphisms and other genetic features may allow for predictive models (33). However, currently there are certain PIDD population-based guidances that can be utilized for optimizing administration and outcome. These are reflected across numerous studies and are illustrated in a recent meta-analysis of reports of IVIG administration in PIDD (34). The purpose of this analysis was to survey existing IVIG studies to extract common endpoints as an efficacy measure in an effort to relate them to dose and or trough. While reporting was found to be variable among distinct studies, there were 17 identified as providing consistent information to be able to evaluate IVIG dosage, IgG trough level and the incidence of pneumonia. This was considered relevant since pneumonia is a major PIDD-associated infection and one that can result in significant morbidity in patients. In aggregate, the included studies had an average of 34 patients each and were comprised of 49% common variable immunodeficiency and 37% X-linked agammaglobulinemia. The remainder of patients was accounted for by a variety of other PIDD diagnoses. While it may not be a surprise, one finding was that IVIG dose correlated with IgG trough (Figure 1). In aggregate, the data demonstrated that for every 100mg/kg dose increase a 121mg/dl trough increase could be expected. What was perhaps more surprising, however, was that for every 100mg/dl trough increment a 27% decrease in pneumonia incidence was identified (Figure 2). Importantly, the pneumonia incidence was not predicted to reach zero at the highest trough levels available from the data set (1000mg/dl).

**FIGURE 1**

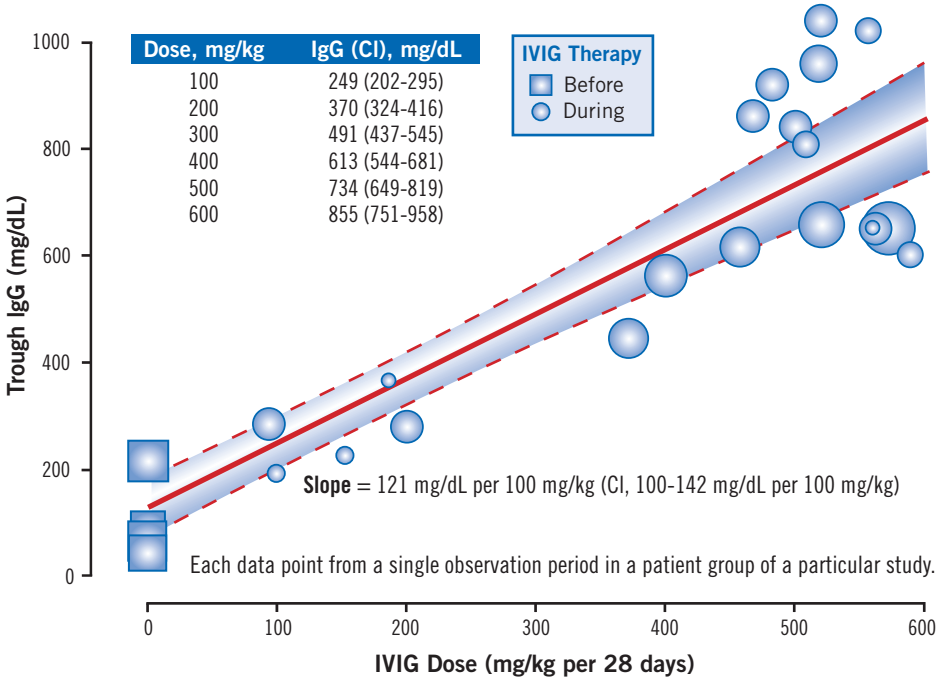


**Figure 1:** IVIG dosage relates to IgG trough level in Meta-analysis. Individual studies from which IVIG dosing information and corresponding IgG trough levels were evaluated and are represented with individual circles or squares. The size of the circle or square corresponds to the patient-years observed in the study. The squares represent the IgG level in the patients from a particular study prior to being started on IVIG therapy and are thus all present at an IVIG dosage of zero. The red line represents multilevel model predictions, and dashed lines indicate the 95% confidence interval (CI) of metaregression for the included studies. Interval values are provided in the inset table Modified from Orange, J.S., et. al., Clinical Immunology 2010, 137:21-30

**FIGURE 2**

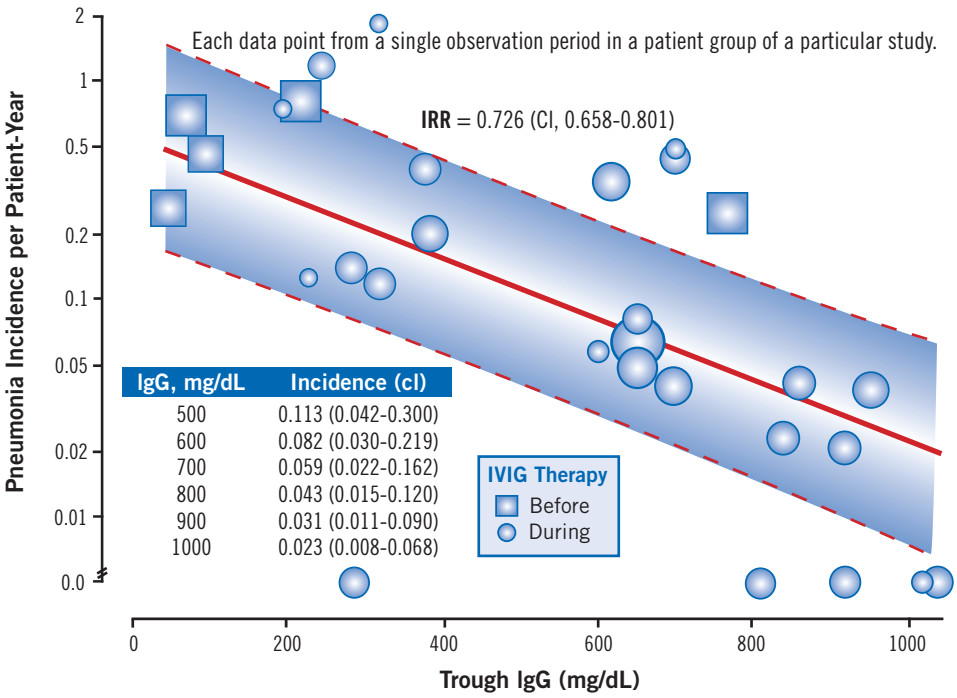


**Figure 2:** IgG trough level relates to pneumonia incidence in Meta-analysis. Data on pneumonia incidence was extracted from the studies depicted in Figure 1 and are represented with individual circles or squares. The size of the circle or square corresponds to the patient-years observed in the study. The squares represent the historical incidence of pneumonia (where reported) in the patients from a particular study prior to being started on IVIG therapy and are thus all present at nominal IgG trough levels. The red line represents multilevel model predictions, and dashed lines indicate the 95% confidence interval (CI) of metaregression for the included studies. Interval values are provided in the inset table Modified from Orange, J.S., et. al., Clinical Immunology 2010, 137:21-30

Similar results concerning pneumonia incidence were obtained when the input value was IVIG dose instead of IgG trough. Another recent report of a large PIDD cohort not included in the meta-analysis derived IgG trough levels required for patients to have <4.5, <2.5 or zero infections per year (35). Interestingly, these authors found a requirement for trough IgG levels similar to those identified at the high end of the meta-analysis.

These new findings suggests that one opportunity to optimize IVIG therapy for a PIDD patient who continues to experience infection despite receiving regular replacement with IVIG, would be to increase the IgG trough level. This can be accomplished either by increasing the IVIG dosage (as shown in the meta-analysis; Figure 1), or by decreasing the interval between doses. This has been challenging for certain patients since their insurance policies sometimes direct specific dosages and trough levels (32). These and related data, will hopefully empower the prescriber to justify this type of optimization in their PIDD patients. These data in no way, however, imply the converse (i.e., that in a patient not experiencing infections the IVIG dose or trough level can be decreased). The data, analyses and studies were not designed to test this approach and specific data collection is warranted before any of this type of adjustment could be considered. This strategy also should be viewed as seriously flawed since in PIDD, experimenting with an "acceptable" infection rate is truly dangerous. The first incidence of infection in a previously well-controlled patient would have the potential to be a fatal infection.

Another potential point for optimization has to do with the IVIG products themselves. There have only been two relatively recent head-to-head comparisons of IVIG products in PIDD. Importantly, these demonstrated relevant differences between the products studied including infection rate and adverse event profiles. Unfortunately, both of these studies had compared a current IVIG product to one that is no longer available (36, 37). More effective and current data are needed. Yet, in the absence of suitable data, it is worth considering that there are differences between individual products that have the potential to impact patients differently. In this light, if a patient is doing poorly on a particular IVIG product and efforts at dose/interval optimization have proven to be of limited value, consideration of a product change may be reasonable. Product changes are also reasonable to consider if a patient is experiencing consistent infusion-related adverse events since again an individual patient may respond differently to a distinct IVIG product (38). It is also reasonable to consider changing the route of Ig administration from IV to SC (this is discussed separately in the next section).

Finally, it is essential to remember that while Ig therapy is important, is is only one of many interventions that can be applied to PIDD patients. It is extremely important to diagnose and manage comorbid conditions such as atopic disease, asthma, inflammatory bowel disease, gastroesophageal reflux and others. Effective diagnosis and management of these conditions has the potential to help reduce incidence of infections and improve quality of life. Another intervention that is commonly applied is the administration of antibiotic prophylaxis (26). Unfortunately, there are no modern data evaluating antibiotic prophylaxis in antibody deficient patients when used as an adjunct to IVIG. The survey of AAAAI members, however, identifies that the vast majority of physicians recommend antibiotic prophylaxis as an adjunct measure to IVIG for at least

some PIDD patients (26). The prophylaxis regimens that physicians reported were highly variable and specific clinical studies are indicated. One additional group of adjunct measures for which there are no data in the context of IVIG administration are complementary therapies such as stress-reducing measures, probiotics, nutritional supplements, and specific hygiene interventions (26). While data exist in other conditions for some of these with regards to reducing incidence of infection or improving immune indices, specific studies in PIDD patients receiving IVIG is warranted. In the meantime, it is reasonable to consider some of these interventions after careful evaluation of their potential physical or psychological risks to the patient.

## Subcutaneous Immunoglobulin

SCIG has been gaining popularity in the U.S. and presents some potential and actual opportunities to optimize PIDD management in certain patients (39, 40). SCIG has been reviewed extensively and is the subject of a stand-alone IDF Clinical Focus document of this series http://www.primaryimmune.org/publications/clinic_focus/cf_feb08.pdf. So for comprehensive consideration of SCIG the reader is referred to the previous clinical focus document. In brief, SCIG is associated with a lower incidence of systemic adverse events, as well as certain quality of life benefits (39, 27, 41-44). SCIG has the disadvantages of requiring more frequent infusion, and causing local infusion site reactions. Patients administering SCIG also need to have the capability to provide self-infusion and manage the process independently of direct medical professional supervision. This is because the most widely applied current model in the U.S. is that the SCIG is provided to patients at home along with equipment they will need to infuse it after they have been adequately trained in SCIG administration procedures. SCIG does present a viable therapeutically equivalent alternative to IVIG and presents specific opportunities for optimizing outcome for some patients. Especially those patients desiring independence from the hospital or home nurse (commonly provided for home-based IVIG therapy), or those having severe systemic adverse events related to IVIG, as well as more mild ones such as headache or nausea.

For patients already on SCIG, specific data to guide optimization are sparse. The U.S. clinical trial for the recently available 20% SCIG product contained a sub-study comparing certain of its properties to the currently available 16% SCIG product (16). Interestingly, the 20% product was found to be significantly better tolerated with regards to patient reported local mean and maximal pain. So, at least for patients who are having difficulty with local pain during SCIG infusion, changing products may present some value. As for dosing regimens, doses and serum IgG levels in patients receiving SCIG, the extent of data found in IVIG therapy does not exist. Presently, physicians are left to extrapolate practice from experience and the data that are available. For one, the rate of infections in the U.S. trial of the 16% SCIG was 4.43 (45), while in the 20% SCIG it was 2.73 (16). This apparent difference is intriguing in light of the fact that the mean patient serum IgG levels for patients on therapy in the two trials was different with a level of 1040mg/dl in the former and 1256mg/dl in the latter. Hopefully future research will define if specific opportunities for optimization of outcome as a feature of dose and regimen will exist for patients receiving SCIG as it appears to for patients receiving IVIG.

## Conclusion

Ig therapy in the PIDD patient represents a life saving and life-altering intervention that should be provided where indicated. Importantly Ig therapy does not represent a binary decision and access to therapy does not imply access to optimal therapy. There are numerous opportunities to adjust, change or add to therapy to optimize and improve PIDD patient outcomes. It is important that the physician be attuned to these possibilities and collaborates with the patient to take advantage of opportunities to improve a patient's coexistence with their disease.


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*The Immune Deficiency Foundation, founded in 1980, is the national patient organization dedicated to improving the diagnosis, treatment and quality of life of persons with primary immunodeficiency diseases through advocacy, education and research.*

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